REMARKS

Status of the Claims

Claims 34-64, 67-70, 73, 79 and 80 were considered in the final Office action mailed on July 19, 2007. As reflected in the listing of claims beginning on page 2 of this paper, Applicants cancel previously presented claims 34-64 and previously withdrawn claims 65, 66 and 74-78 herein without prejudice to later reintroducing their subject matter. Following entry of the amendments, claims 67-70, 73, 79 and 80 will be pending for the Examiner's consideration.

Summary of the Claimed Invention

The core of the present invention is the discovery that mutations in the MRP6 gene are associated with PXE. The genomic sequence of the MRP6 gene is provided in the specification at SEQ ID NO:1 and Applicants provide extensive clinical and biochemical evidence throughout the specification supporting the conclusion that several specific mutations in the MRP6 gene are associated with PXE.

Independent claims 67, 68 and 73 are directed to methods of screening a patient for an increased risk of having children with PXE, for an increased risk of developing a PXE associated symptom, and for the presence of a PXE mutation, respectively. According to these methods, an MRP6 nucleic acid in a patient sample is interrogated for the presence of a mutation known to be a co-segregator with a PXE phenotype and identifying the patient as having said risk if the mutation or allele is detected in the MRP6 nucleic acid.

Independent claim 79 is directed to a method for detecting a patient having an increased risk of developing PXE by interrogating an MRP6 nucleic acid of the patient and determining an abnormal presence or absence of at least one nucleic acid fragment or sequence in the patient's MRP6 nucleic acid compared to a normal control.

Independent claim 80 is directed to a method for screening a patient for the presence of a MRP6 gene mutation. This method comprises in part interrogating an MRP6 nucleic acid in a

patient sample to determine an MRP6 nucleic acid sequence and comparing the MRP6 nucleic acid sequence from step a) to a normal MRP6 nucleic acid sequence.

Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement

Claims 34-63 and 67-72 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to enable one skilled in the art to make and/or use the invention without undue experimentation. Specifically, the Examiner alleges that, although the specification teaches several specific PXE mutations, the specification does not enable interrogating an MRP6 nucleic acid for the presence of any PXE mutation. Therefore, according to the Examiner, one of ordinary skill in the art would need to undertake undue experimentation and test hundreds, if not thousands, of possible nucleotide alterations throughout the MRP6 gene to determine which mutations are PXE mutations. See, Office action at pages 2-11.

Applicants note that the Examiner's comments in the Detailed Action section of the final Office action dated July 17, 2007 refer to the claims as presented in the original application as filed and do not specifically refer to the claims as amended in Applicants' Amendment and Response filed on April 27, 2007. Specifically, the Examiner does not refer to the language of claims 67 and 68 as amended, for example, the method for identifying a patient as having an increased risk of developing PXE. Although Applicants cancel claims 34-63 herein, Applicants will address the rejection with respect to pending claims 67-72.

Applicants submit that the present specification fully enables one of skill in the art to determine if a mutation in an MRP6 gene is a co-segregator with a PXE phenotype as recited in independent claims 67 and 68. The specification of the present application provides reasonable guidance or direction on how to practice the claimed invention. For example, the specification teaches a variety of methods for detecting mutations in the MRP6 gene, *e.g.*, at paragraphs [0037] and [0149]-[0163]. The specification further teaches methods to determine if a mutation is a co-segregator with a PXE phenotype using multi-generational pedigree analysis, *e.g.*, at paragraphs [0182]-[0185]. One of skill in the art upon review of the recited paragraphs would readily have understood how to carry out nucleic acid assays and co-segregation analysis in order to determine if a mutation in an MRP6 gene co-segregates with a PXE phenotype.

Applicants submit that experimentation, particularly when routine and thoroughly disclosed, is permissible. The court in *In re* Wands stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" 858 F.2d 731, 736-737 (Fed. Cir. 1988). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 737. Applicants submit that because (1) the disclosure teaches considerable direction and guidance on how to practice the invention, (2) the disclosure teaches several working examples, (3) there was a high level of skill in the art at the time when the application was filed, and (4) all of the methods needed to practice the invention were disclosed or well known, undue experimentation is not required to practice the claimed invention.

Thus, in view of the teachings of the present application and armed with the knowledge available in the art, one of ordinary skill readily would have been able to detect a PXE mutation in a patient by establishing if a mutation in an MRP6 gene is associated with PXE by determining if a mutation is a co-segregator with a PXE phenotype.

Applicants further submit that the knowledge of a specific mutation in the MRP6 gene is not required to practice the invention as recited in independent claims 67 and 68. Claims 67 and 68 are directed to a method for detecting a patient having an increased risk of developing PXE. In other words, claims 67 and 68 only require detecting a patient who is more likely to develop PXE than a normal patient. Applicants submit that claims 67 and 68 do not require detecting a specific mutation in a patient's MRP6 gene in order to determine that the patient is more likely to develop PXE than a normal patient. Detection of a mutation manifested by at least one abnormal nucleic acid fragment or sequence in a patient's MRP6 gene would be sufficient to indicate that the patient is more likely to develop PXE than a normal patient because an MRP6 gene containing an abnormal nucleic acid fragment or sequence is more likely to have an abnormal MRP6 protein compared to a normal MRP6 gene. Similar correlation between defects in genes without knowledge of the specific mutation and disease is known in the medical arts. For

example, it is well accepted that an individual is more likely to develop cancer than a normal individual if the individual's p53 gene (tumor suppressor gene) contains a mutation (*i.e.*, abnormal nucleic acid fragment or sequence) compared to a normal control, even if the specific nature of the mutation is unknown.

Therefore, Applicants submit that the nature of the invention as claimed in independent claims 67 and 68 does not require the knowledge of a specific mutation. It only requires determination of abnormal presence or absence of at least one nucleic acid fragment or sequence in a patient's MRP6 gene compared to a normal control.

For at least the above reasons, Applicants respectfully submit that the present application fully complies with the enablement requirement with respect to independent claims 67 and 68, and their dependent claims 69-70, and request reconsideration and withdrawal of the rejections of claims 67-72 under 35 U.S.C. § 112, First Paragraph.

Double Patenting Rejection

Claims 34-64, 67-73 and 79-80 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,780,587.

Applicants will present a Terminal Disclaimer once one or more claims are found allowable, disclaiming the terminal part of any patent granted on U.S. Serial No. 10/764,328 which would extend beyond the full statutory term of U.S. Patent No. 6,780,587. Applicants note that claims 73, 79 and 80 were not rejected on grounds other than double patenting. Accordingly, Applicants request that the Examiner indicate claims 73, 79 and 80 would be found allowable in the event a Terminal Disclaimer is filed.

Applicants submit that the filing of a Terminal Disclaimer will obviate the double patenting rejection and respectfully request reconsideration and withdrawal of the rejection.

Conclusion

In view of the foregoing remarks, Applicants respectfully request allowance of claims 67-70, 73, 79 and 80. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney.

Respectfully submitted,

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Karen A. Schouten
Attorney for Applicant(s)
Kirkpatrick & Lockhart Preston
Gates Ellis LLP
State Street Financial Center
One Lincoln Street
Boston, Massachusetts 02111-2950

Tel. No.: (617) 261-3216
Fax No.: (617) 261-3175